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(12) # EUROPEAN PATENT APPLICATION

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(54) **Pharmaceutical preparation comprising coated capsules or tablets containing a liposome powder encapsulating a drug**

(57) A new pharmaceutical preparation to improve the oral bioavailability of difficult-to-absorb drugs comprising capsules or tablets coated with enteric material containing a freeze-dried or evaporated liposome powder incorporating a drug of pharmacological benefit.

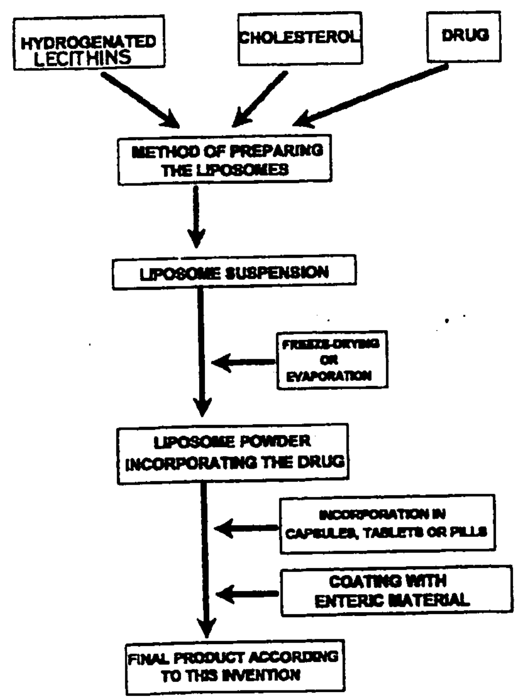

FIG. 1

EP 0 855 179 A2

Description

Scope of the invention

This invention relates to a new composition for improving the absorption of orally administered drugs.

The composition according to the invention is obtained by incorporating the drug in liposomes comprising hydrogenated lecithin and cholesterol, followed by evaporation or freeze-drying of the solvent in which the liposomes are suspended.

The resulting liposome powder is administered orally, in a capsule or tablet, protected in its passage through the stomach by an enteric coating.

Basis of the invention

The oral route is the preferred route for the administration of drugs of all kinds to patients because of the advantages offered by this type of administration in comparison with other more aggressive routes and/or routes which are of more difficult application (endovenous, parenteral, subcutaneous, etc.).

Nevertheless, not all drugs are satisfactorily absorbed via the gastrointestinal tract. This absorption depends, among other factors, on the permeability of the gastrointestinal mucosa to the drug and on the acid and/or enzyme degradation processes to which the drug is subjected during its residence time in the gastrointestinal tract.

It is therefore obvious that any factor which improves the rate of absorption of the drug or which protects it from the degradative processes mentioned will improve the clinical efficacy of the drug.

State of the Art

Great efforts have been made recently to identify agents which are capable of increasing the permeability of the gastrointestinal mucosa to poorly absorbed materials: surfactants (George, Sutter, Finegold, J. Infect. Dis. 136, 822 (1977)), chelating agents (Cassidy, Tidball, J. Cell. Biol. 32, 672 (1967)), salicylates (Higuchi, et al., U.S. Patent 4,462,991 (1984)), anti-inflammatories (Yaginuma, et al., Chem. Pharm. Bull. 29, 1974 (1961)), phenothiazines (Alexander and Fix, U.S. Patent 4,425,337 (1984)), acyl carnitines (Alexander and Fix, USSN 606,054), and fatty acids (Yamazaki, et al., J. Pharm. Pharmacol., 42, 441, (1990)) have been described as being capable of increasing the gastrointestinal permeability of a great variety of compounds. On the other hand, the effort to produce systems which protect a drug from gastrointestinal degradative processes has also been very considerable. Amylose coatings (WO 89/11269), lactic and glycolic acid polymers (EP 0202159), calcium alginate (Chong-Kook K., Eun-Jin L., Int. J. Pharm., 79, 11 (1992)), and polymerized liposomes (WO 95/03035) have been described as systems for the administration of drugs via the gastrointestinal route.

Summary of the Invention

As a result of the research work carried out it has now been surprisingly found that the bioavailability of drugs which are difficult to absorb via the gastrointestinal route is greatly increased when they are administered orally incorporated in freeze-dried liposomes, provided that this freeze-dried liposome preparation is administered in capsules or tablets provided with an enteric coating which enables them to withstand the acid environment of the stomach.

The subject matter of this invention therefore comprises a new system for the oral administration of drugs obtained by incorporating a drug in liposomes comprising hydrogenated lecithins and cholesterol, subsequently freeze-dried or evaporated to dryness to obtain a powder, which is administered orally in tablets or capsules provided with a coating of enteric material which makes it possible to release the contents of these capsules or tablets after they have passed through the stomach.

These formulations have the inherent advantages of oral administration in comparison with other kinds of administration, that is, these formulations are easier to administer, more convenient, less aggressive and better tolerated by patients.

Detailed description of the invention

Lecithins are mixtures of phospholipids obtained by extraction from natural products such as eggs (egg lecithins), soya (soya lecithins), etc. These natural lecithins are in fact mixtures of phospholipids comprising fatty acids of different chain length and different degrees of saturation.

In this invention hydrogenated lecithins are taken to mean lecithins obtained from natural sources (such as eggs, soya, etc.) which have been subjected to a catalytic hydrogenation process with a view to reducing their degree of

unsaturation to a very low level (iodine number not greater than 2 g/100 g).

The constituent lipids of the liposomes comprising the system according to this invention comprise a mixture of hydrogenated lecithins and cholesterol.

The processes for obtaining liposomes and incorporating the drugs in these liposomes, which is required in order to obtain the system according to this invention, are well-known and described in the state of the art (see, e.g.: Szoka F. and Papahadjopoulos, D., Ann. Rev. Biophys. Bioeng. 9 (1980) 467-508).

Appended Figure 1 shows a flow diagram of the process for obtaining the composition according to this invention.

The materials which can be used to manufacture the enteric coating for the capsules or tablets to which this invention relates are widely known in the state of the art and are commonly used in the pharmaceutical field to produce enteric coatings for capsules and tablets, such as, e.g. seals based on acrylic resins (acrylic acid copolymers with acrylic acid esters), e.g. Eudragit L, Eudragit S, Eudragit RL or Eudragit RS, etc., and seals based on cellulose derivatives such as cellulose acetophthalate, etc.

The drugs which can be incorporated in the new drug administration system according to the invention comprise, but are not restricted to:

- antibacterial drugs such as gentamycin, quinolones such as the cyprofloxacine, penicillins, or cephalosporins,
- antiviral agents such as rifampacin or acyclovir,
- antifungal compounds such as amphotericin B, myconazole, terconazole, econazole, isoconazole, thioconazole, biphonazole, clotrimazole, ketoconazole, butaconazole, itraconazole, oxyconazole, fenticonazole, nystatin, naftifine, zinoconazole, cyclopyroxolamine and fluconazole,
- anti-parasitic compounds such as antimony derivatives,
- anti-tumor and anti-neoplasm compounds such as adriamycin, vinblastine, vincrystine, mitomycin C, doxorubicin, daunorubicin, methotrexate, cisplatin and others,
- antimetabolites,
- proteins such as albumin,
- toxins such as diphtheria toxin,
- enzymes such as catalase,
- peptides like hirudin, somatostatin or thymopentin,
- hormones such as estrogen, progesterone or estradiol,
- synthetic estrogens and progestogens like 17-ethynyl estradiol, etc.,
- peptide hormones such as human growth hormone, porcine growth hormone, bovine growth hormone, human calcitonin, salmon calcitonin, carbocalcitonin, insulin or LHRH and analogs,
- hormone antagonists,
- neurotransmitters like acetylcholine,
- neurotransmitter antagonists,
- glycoproteins like hyaluronic acid,
- lipoproteins like alpha-lipoprotein,
- immunoglobulins such as IgG,
- immunity modulators such as interferon, interleukin,
- immunosurpressors such as cyclosporin A,
- vasodilators,
- coloring agents like Arsenazo III,
- radioactive markers like ^{14}C,
- radio-opaque compounds such as ^{90}Te,
- fluorescent compounds such as carboxyfluorescein,
- cell receptors such as the estrogen receptor protein,
- non-steroid anti-inflammatories such as indomethacin, ibuprofen, sulindac, pyroxycam, naproxen, nimesulide or ketorolac,
- anti-inflammatories such as dexamethasone,
- anti-glaucoma agents such as pilocarpine or thymolol,
- mydriatic compounds,
- local anesthetics such as lidocaine,
- narcotics such as codeine,
- vitamins such as alpha-tocopherol, vitamin B_{12},
- nucleic acids such as thymine,
- polynucleotides such as RNA,
- psychoactive and anxiolytic compounds such as diazepam,
- mono-, di- and polysaccharides such as glycogen,

- glycosaminoglycanes such as unfractionated heparins, low molecular weight heparins, very low molecular weight heparins, pentasaccharide, dermatan sulfate, heparin sulfate, chondroitin-4-sulfate, chondroitin-6-sulfate and derivatives,
- cardiovascular agents such as alpha-blockers, beta-blockers, calcium channel blockers, ACE inhibitors, histamine H2 receptor inhibitors or serotonin H3T receptor inhibitors,
- diphosphonates such as alendronic acid and their salts,
- prostaglandins,
- mineral salts having pharmacological activity, such as iron (II) sulfate, sodium fluoride, etc.

The invention will now be described purely by way of illustration and not in any restrictive way by means of the following examples.

EXAMPLE 1: PREPARATION OF FREEZE-DRIED LIPOSOME CAPSULES CONTAINING SODIUM ALENDRONATE

A mixture comprising 1244.2 mg of hydrogenated egg lecithin and 499.7 mg of cholesterol was dissolved in 200 ml of chloroform/methanol (75/25). The organic solvents were then removed by rotary evaporation, and traces of solvent were also removed by the passage of N_2 or by freeze-drying. The lipid film obtained in this way was hydrated using 50 ml of 0.9% NaCl solution containing 264.1 mg of sodium alendronate, by agitation in a vibromixer at intervals of 30 seconds, followed by standing in a bath kept at 60°C for the same length of time until the total effective agitation time was 10 minutes, a liposome suspension being obtained in this way.

The resulting liposome suspension was frozen and freeze-dried to obtain a freeze-dried powder which was placed in hard gelatin capsules (50 mg of freeze-dried preparation in each gelatin capsule). The resulting capsules were coated with an enteric polymer (EUDRAGIT-L) by repeated immersion in a solution of the enteric polymer in isopropanol and subsequent drying in a current of air.

EXAMPLE 2: PREPARATION OF FREEZE-DRIED LIPOSOME CAPSULES CONTAINING NIMESULIDE

1.25 g of nimesulide were suspended in 100 ml of distilled water. A mixture comprising 800 mg of cholesterol and 800 mg of hydrogenated lecithin was added slowly to the resulting suspension with vigorous agitation. The resulting suspension was heated to 60°C and kept under agitation until no further nimesulide particles could be seen in suspension and the lipids were totally hydrated, yielding a suspension of liposomes incorporating nimesulide.

The resulting liposome suspension was frozen and freeze-dried to obtain a freeze-dried preparation which was placed in hard gelatin capsules (114 mg of freeze-dried preparation in each gelatin capsule). The resulting capsules were coated with an enteric polymer (EUDRAGIT-L) by repeated immersion in a solution of the enteric polymer in isopropanol and subsequent drying in a current of air.

EXAMPLE 3: PREPARATION OF FREEZE-DRIED LIPOSOME CAPSULES CONTAINING PROGESTERONE

4.01 g of progesterone were suspended in 400 ml of distilled water. A mixture comprising 6.67 g of hydrogenated lecithin and 2.71 g of cholesterol was added slowly to the resulting suspension with vigorous agitation. The resulting suspension was kept under agitation until hydration of the lipids was complete and a liposome suspension was obtained.

The resulting liposome suspension was frozen and freeze-dried to obtain a freeze-dried powder which was placed in hard gelatin capsules (333 mg of freeze-dried preparation in each gelatin capsule). The resulting capsules were coated with an enteric polymer (EUDRAGIT-L) by repeated immersion in a solution of the enteric polymer in isopropanol and subsequent drying in a current of air.

EXAMPLE 4: PREPARATION OF FREEZE-DRIED LIPOSOME CAPSULES CONTAINING PROGESTERONE

6.67 g of hydrogenated lecithin and 2.71 g of cholesterol were dissolved in 500 ml of chloroform/methanol (75/25). The organic solvents were then removed by rotary evaporation, and traces of solvent were also removed by the passage of N_2 or freeze-drying. The lipid film obtained in this way was hydrated using 200 ml of water by agitation in a vibromixer at intervals of 30 seconds followed by standing in a bath kept at 60°C for the same length of time until the total effective agitation time was 10 minutes, a liposome suspension being obtained in this way. 4.01 g of progesterone were added to the liposome suspension and the resulting system was incubated at 60°C for 24 hours in order to incorporate the drug into the liposomes.

The liposome suspension resulting from the incubation was frozen and freeze-dried to obtain a freeze-dried prep-

aration which was placed in hard gelatin capsules (333 mg of freeze-dried preparation in each gelatin capsule). The resulting capsules were coated with an enteric polymer (cellulose acetophthalate) by repeated immersion in a solution of the enteric polymer in isopropanol and subsequent drying in a current of air.

EXAMPLE 5: PREPARATION OF LIPOSOME CAPSULES CONTAINING IRON (II) Sulfate

2.4 g of $FeSO_4.17H_2O$, 31 mg of ascorbic acid and 31 mg of cysteine were suspended in 100 ml of distilled water. A mixture comprising 800 mg of cholesterol, 800 mg of hydrogenated lecithin and 31 mg of vitamin E acetate was added slowly to the resulting suspension with vigorous agitation. The resulting suspension was heated to 60°C and was kept under agitation under a nitrogen atmosphere until the lipids were totally hydrated, a suspension of liposomes incorporating iron sulfate being obtained.

The resulting liposome suspension was evaporated to dryness to obtain a solid which was placed in hard gelatin capsules (510 mg of solid in each gelatin capsule). The resulting capsules were coated with an enteric polymer (EUDRAGIT-L) by repeated immersion in a solution of the enteric polymer in isopropanol, and subsequent drying in a current of air.

EXAMPLE 6: PREPARATION OF FREEZE-DRIED LIPOSOME CAPSULES CONTAINING SODIUM FLUORIDE

2.05 g of sodium fluoride (NaF) were dissolved in 552 ml of distilled water. A mixture comprising 13.8 g of hydrogenated lecithin and 5.27 g of cholesterol was added slowly to the resulting solution with vigorous agitation. The resulting suspension was kept under agitation until hydration of the lipids was complete.

The resulting liposome suspension was frozen and freeze-dried to obtain a freeze-dried powder which was placed in hard gelatin capsules (100 mg of freeze-dried preparation in each gelatin capsule). The resulting capsules were coated with an enteric polymer (EUDRAGIT-L) by repeated immersion in a solution of the enteric polymer in isopropanol and subsequent drying in a current of air.

EXAMPLE 7: PREPARATION OF FREEZE-DRIED LIPOSOME CAPSULES CONTAINING ETHYNYL Estradiol

18 mg of ethynyl estradiol were suspended in 400 ml of distilled water. A mixture comprising 4.49 g of hydrogenated egg lecithin and 4.49 g of cholesterol was added slowly to the resulting suspension with vigorous agitation. The resulting suspension was kept under agitation until hydration of the lipids was complete and a liposome suspension was obtained.

The resulting suspension was incubated at 60°C for 24 hours to encourage incorporation of the ethynyl estradiol into the liposomes, and subsequently the liposome suspension was frozen and freeze-dried to obtain a freeze-dried powder which was placed in hard gelatin capsules (7.2 mg of freeze-dried preparation in each gelatin capsule). The resulting capsules were coated with an enteric polymer (EUDRAGIT-RL) by repeated immersion in a solution of the enteric polymer in isopropanol and subsequent drying in a current of air.

EXAMPLE 8: COMPARATIVE INVESTIGATION OF BLOOD NIMESULIDE LEVELS AFTER THE ADMINISTRATION OF A SINGLE ORAL DOSE OF CAPSULES CONTAINING 50 mg OF NIMESULIDE AND THE CAPSULES OBTAINED IN EXAMPLE 2

The investigation was performed to compare blood nimesulide levels after the oral administration of a single dose of 50 mg of nimesulide to humans in the following forms:

- GROUP A: Hard gelatin capsules containing 50 mg of nimesulide.
- GROUP B: The capsules obtained in EXAMPLE 2.

Blood nimesulide levels were analyzed on samples taken at the following times after administration: 0, 0.25, 0.5, 0.75, 1, 2, 3, 4 and 5 hours.

The analytical method used for the analysis of nimesulide in biological samples (plasma) was based on a process of semi-automatic purification of the sample (HPLC with column-switching).

The biological samples were deproteinized using methanol and perchloric acid, the protein precipitate being separated out by centrifuging, and a specific volume of the supernatant plasma being injected. After injection into the HPLC, the sample was initially purified by passing through a Spherisorb C18 column (30 x 4.6 mm I.D., 5 µm) for six minutes, with 0.05 M pH5 phosphate buffer/acetonitrile (80/20) as eluent. This was subsequently automatically introduced into the analytical column (Waters Nova-pack C18, 150 x 3.9 mm I.D., 5 µm) via the switching valve. The eluent used in the analysis comprised 0.5 M pH5 phosphate buffer/methanol (45/55).

Signal intensity was read using an ultraviolet detector at 302 nm.

The results of the analysis are detailed in the following table and in the graph in appended Figure 2.

	TIME IN HOURS								
	0	0.25	0.5	0.75	1	2	3	4	5
GROUP A (µg/ml)	0	0	1.134	1.5093	2.4769	3.6514	1.9487	2.1233	2.6932
GROUP B (µg/ml)	0	0	0	0.4108	0.9222	6.6049	7.2646	7.3012	7.3166

EXAMPLE 9: INVESTIGATION OF BLOOD PROGESTERONE LEVELS AFTER THE ADMINISTRATION OF A SINGLE ORAL DOSE OF THE CAPSULES OBTAINED IN EXAMPLE 3

The investigation was performed to evaluate blood progesterone levels after the oral administration of a single dose of the capsules prepared in Example 3 to humans.

Blood progesterone levels were analyzed on samples taken at the following times after administration: 0, 0.5, 1, 2, 4, 8, 12 and 24 hours.

The analytical method used for the analysis of progesterone in biological samples (plasma) was based on an HPLC process.

The biological samples were deproteinized with methanol and perchloric acid, the protein precipitate being separated out by centrifuging, and a specific volume of the supernatant plasma being injected after filtration.

The chromatographic conditions for analysis were as follows:

Column: NUCLEOSIL 5 C18 150 mm x 4.6 mm I.D.
Mobile phase: acetonitrile/water 65/35
Flow rate: 1 ml/min
Detection: U.V. 240 nm

The analytical results are indicated in the following table and in the graph in appended Figure 3.

	TIME IN HOURS						
	0	1	2	4	8	12	24
Subject 1 (µg/ml)	0.5	0.5	0.6	4	2.5	1	0.5
Subject 2 (µg/ml)	0.5	0.5	24	6	3	2	0.5
Subject 3 (µg/ml)	0.5	5	18	8.5	10	1.5	0.6
Subject 4 (µg/ml)	0.5	5	16	19.5	2.5	2	0.5
Subject 5 (µg/ml)	0.5	2.5	11	15	3.5	1.7	0.6
Subject 6 (µg/ml)	0.5	2	9.5	6	2	7.5	6.5

EXAMPLE 10: INVESTIGATION OF BLOOD ETHYNYL ESTRADIOL LEVELS FOLLOWING THE ORAL ADMINISTRATION OF A SINGLE DOSE OF THE CAPSULES OBTAINED IN EXAMPLE 7

The investigation was performed to evaluate blood ethynyl estradiol levels after the oral administration of a single dose of the capsules prepared in Example 7 to humans.

Blood ethynyl estradiol levels were analyzed on samples taken at the following times after administration: 0, 0.5, 1, 2, 4, 8, 12 and 24 hours.

The analytical method used for the analysis of ethynyl estradiol in biological samples (plasma) was based on an HPLC process.

The biological samples were deproteinized with methanol and perchloric acid, the protein precipitate being separated out by centrifuging, and a specific volume of the supernatant plasma being injected after filtration.

The chromatographic conditions for analysis were as follows:

Column: NUCLEOSIL 5 C18 250 mm x 4.6 mm I.D.
Mobile phase: acetonitrile/THF/water 12.9/22.4/64.7
Flow rate: 1 ml/min
Detection: U.V. 240 nm

The analytical results are indicated in the following table:

	TIME IN HOURS						
	0	1	2	4	8	12	24
Subject 1 (µg/ml)	40	65	75	68	59	82	48
Subject 2 (µg/ml)	30	55	58	70	82	60	45
Subject 3 (µg/ml)	45	55	41	67	70	83	41
Subject 4 (µg/ml)	47	51	41	65	65	62	52
Subject 5 (µg/ml)	40	52	55	69	73	68	55

Claims

1. A pharmaceutical preparation for oral administration which comprises capsules or tablets coated with enteric material containing a freeze-dried or evaporated liposome powder incorporating a drug of pharmacological benefit.

2. The pharmaceutical preparation as claimed in claim 1, wherein the lipids used in obtaining these liposomes comprise a mixture of cholesterol and hydrogenated natural lecthins (preferably hydrogenated egg lecithin and hydrogenated soya lecithin and their mixtures) having an iodine number not greater than 2 g/100 g.

3. The pharmaceutical preparation as claimed in claims 1 and 2, wherein the enteric agents used are those normally used in the pharmaceutical field to produce enteric coatings for capsules and tablets, preferably seals based on acrylic resins (acrylic acid copolymers with acrylic acid esters) such as Eudragit L, Eudragit S, Eudragit RL or Eudragit RS, and seals based on cellulose derivatives such as cellulose acetophthalate.

4. The pharmaceutical preparation as claimed in claims 1, 2 and 3, wherein the incorporated drugs are:

   - antibacterial drugs such as gentamycin, quinolones such as the cyprofloxacine, penicillins, or cephalosporins,
   - antiviral agents such as rifampacin or acyclovir,
   - antifungal agents such as amphotericin B, myconazole, terconazole, econazole, isoconazole, thioconazole, biphonazole, clotrimazole, ketoconazole, butaconazole, itraconazole, oxyconazole, fenticonazole, nystatin, naftifine, zinoconazole, cyclopyroxolamine and fluconazole,
   - anti-parasitic compounds such as antimony derivatives,
   - anti-tumor and anti-neoplasm compounds such as adriamycin, vinblastine, vincrystine, mitomycin C, doxorubicin, daunorubicin, methotrexate, cisplatin and others,
   - antimetabolites,
   - proteins such as albumin,
   - toxins such as diphtheria toxin,
   - enzymes such as catalase,
   - peptides like hirudin, somatostatin or thymopentin,
   - hormones such as estrogen, progesterone or estradiol,
   - synthetic estrogens and progestogens like 17-ethynyl estradiol, etc.,
   - peptide hormones such as human growth hormone, porcine growth hormone, bovine growth hormone, human calcitonin, salmon calcitonin, carbocalcitonin, insulin or LHRH and analogs,
   - hormone antagonists,
   - neurotransmitters like acetylcholine,

- neurotransmitter antagonists,
- glycoproteins like hyaluronic acid,
- lipoproteins like alpha-lipoprotein,
- immunoglobulins such as IgG,
- immunity modulators such as interferon, interleukin,
- immunosurpressors such as cyclosporin A,
- vasodilators,
- coloring agents like Arsenazo III,
- radioactive markers like ^{14}C,
- radio-opaque compounds such as ^{90}Te,
- fluorescent compounds such as carboxyfluorescein,
- cell receptors such as the estrogen receptor protein,
- non-steroid anti-inflammatories such as indomethacin, ibuprofen, sulindac, pyroxycam, naproxen, nimesulide or ketorolac,

NIMESULIDE

- anti-inflammatories such as dexamethasone,
- anti-glaucoma agents such as pilocarpine or thymolol,
- mydriatic compounds,
- local anesthetics such as lidocaine,
- narcotics such as codeine,
- vitamins such as alpha-tocopherol, vitamin B_{12},
- nucleic acids such as thymine,
- polynucleotides such as RNA,
- psychoactive and anxiolytic compounds such as diazepam,
- mono-, di- and polysaccharides such as glycogen,
- glycosaminoglycanes such as unfractionated heparins, low molecular weight heparins, very low molecular weight heparins, pentasaccharide, dermatan sulfate, heparin sulfate, chondroitin-4-sulfate, chondroitin-6-sulfate and derivatives,

chond sulf

- cardiovascular agents such as alpha-blockers, beta-blockers, calcium channel blockers, ACE inhibitors, histamine H2 receptor inhibitors or serotonin H3T receptor inhibitors,
- diphosphonates such as alendronic acid and their salts,
- prostaglandins,
- mineral salts having pharmacological activity, such as iron (II) sulfate, sodium fluoride, etc.

5. The pharmaceutical preparation as claimed in claims 1, 2, 3 and 4, wherein the lipids used to obtain these liposomes comprise a mixture of cholesterol and hydrogenated natural lecithins in which the proportion of cholesterol varies between 0 and 75%, and more specifically between 24% and 51%.

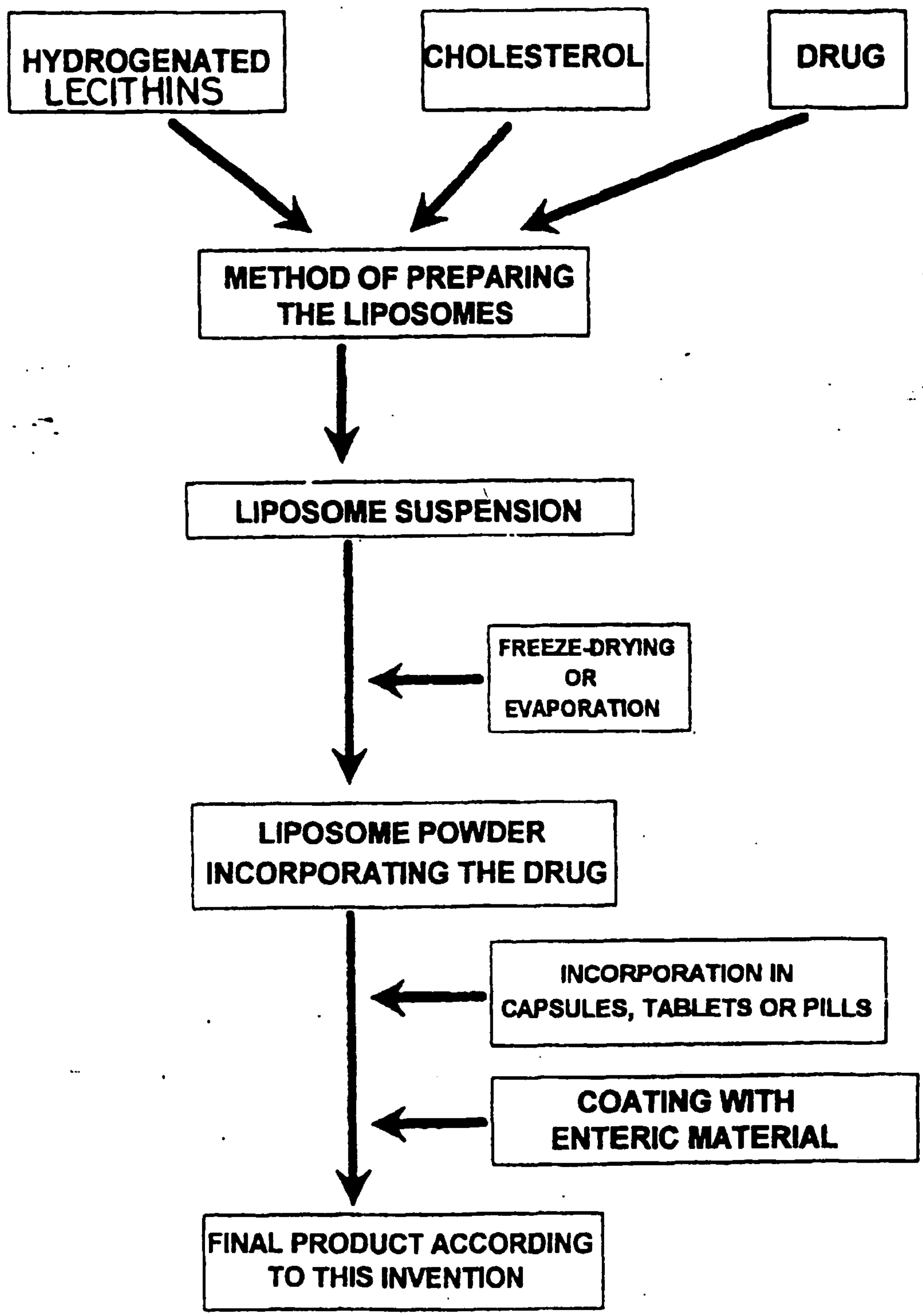
HYDROGENATED LECITHINS
CHOLESTEROL
DRUG
METHOD OF PREPARING THE LIPOSOMES
LIPOSOME SUSPENSION
FREEZE-DRYING OR EVAPORATION
LIPOSOME POWDER INCORPORATING THE DRUG
INCORPORATION IN CAPSULES, TABLETS OR PILLS
COATING WITH ENTERIC MATERIAL
FINAL PRODUCT ACCORDING TO THIS INVENTION

FIG. 1

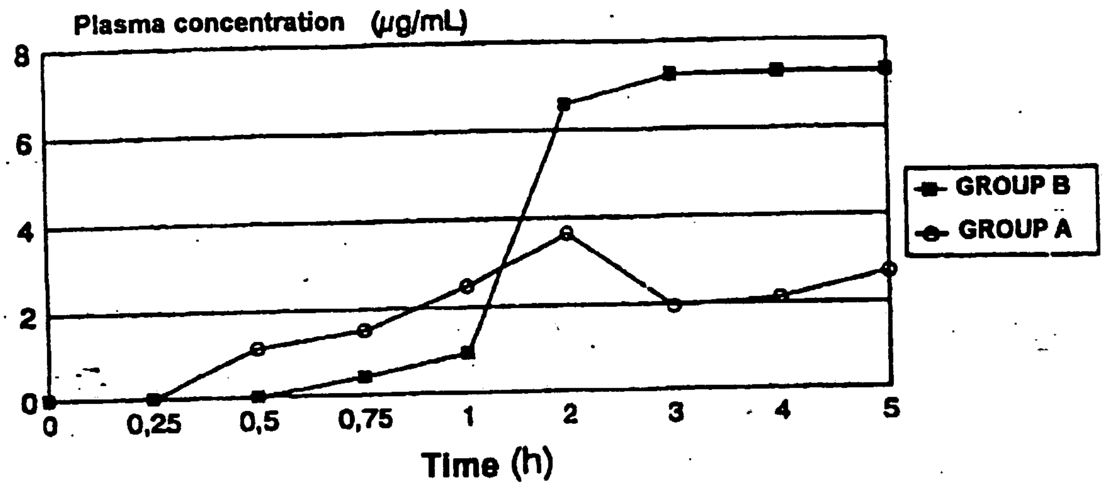
Plasma concentration (µg/mL)
8
6
4
2
0
0
0,25
0,5
0,75
1
2
3
4
5
Time (h)
GROUP B
GROUP A

FIG. 2

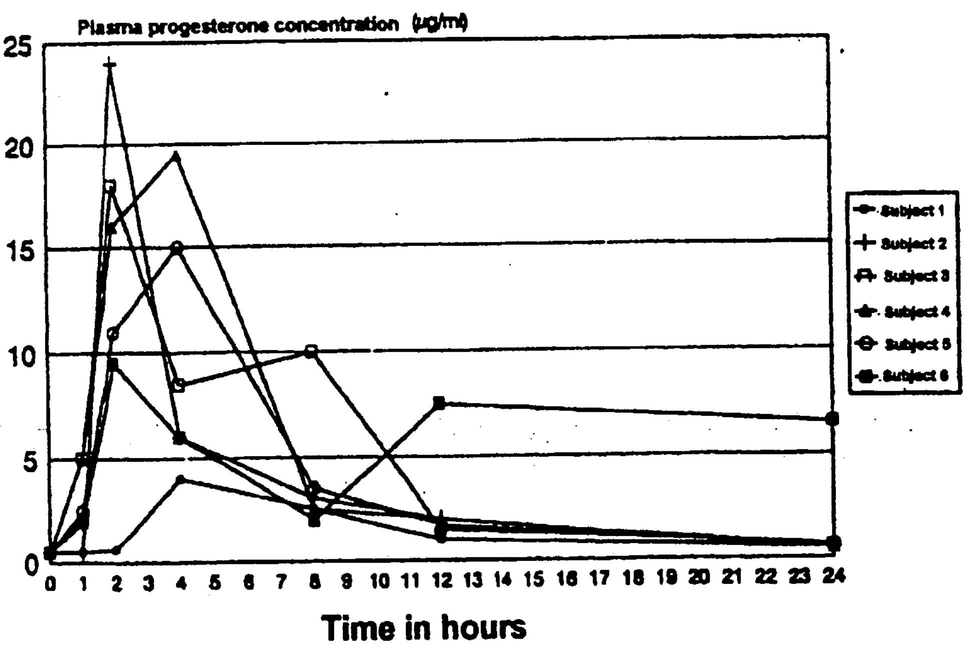
Plasma progesterone concentration (µg/ml)
25
20
15
10
5
0
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24
Time in hours
Subject 1
Subject 2
Subject 3
Subject 4
Subject 5
Subject 6

FIG. 3

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(57) A new pharmaceutical preparation to improve the oral bioavailability of difficult-to-absorb drugs comprising capsules or tablets coated with enteric material containing a freeze-dried or evaporated liposome powder incorporating a drug of pharmacological benefit.

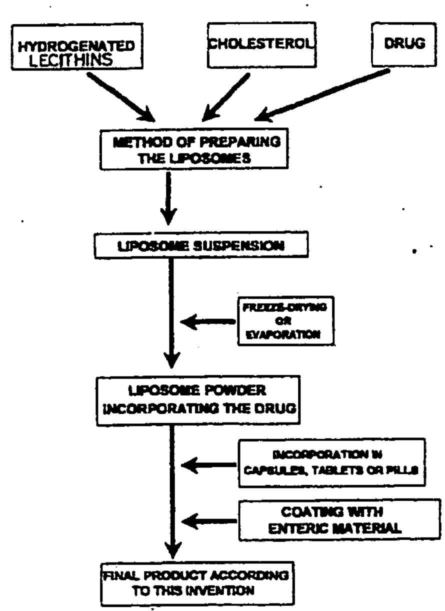

FIG. 1

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European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 97 50 0231

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	DATABASE WPI Section Ch, Week 8918 Derwent Publications Ltd., London, GB; Class B03, AN 89-132542 XP002091456 & JP 01 075421 A (SAWAI SEIYAKU KK) , 22 March 1989 * abstract * ---	1-5	A61K9/127 A61K9/48
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Place of search	Date of completion of the search	Examiner
MUNICH	28 January 1999	Stoltner, A

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